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A METHOD OF PREPARING A COLLAGEN SPONGE, A DEVICE FOR EXTRACTING A PART OF A COLLAGEN FOAM, AND AN ELONGATED COLLAGEN SPONGE

CLAIM OF PRIORITY UNDER 35 USC 119

Assistant Commissioner for Patents,
Washington, DC 20231

Sir:

Applicant in the above-entitled application hereby claims the date of priority under the International Convention of Danish Patent Application No. PA 2001 00135, filed January 25, 2001, as acknowledged in the Declaration of this application.

A certified copy of said Danish Patent Application is submitted herewith.

Respectfully submitted,

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The attached photocopy is a true copy of the following document:

- The specification, claims and figures as filed with the application on the filing date indicated above.

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Head Clerk

A METHOD OF PREPARING A COLLAGEN SPONGE, A DEVICE FOR EXTRACTING A PART OF A COLLAGEN FOAM, AND AN ELONGATED COLLAGEN SPONGE

TECHNICAL FIELD

The present invention relates to a method of preparing a collagen sponge. The collagen sponge produced according to the invention is in particular useful in surgery primarily to stop capillary bleeding. The collagen sponge may also be used as a carrier to be coated with a fibrin glue preparation. The invention also relates to a device for extracting a part of a collagen foam. The invention further relates to an elongated collagen sponge, primarily for gastrointestinal use.

BACKGROUND OF THE INVENTION

Collagen has been used as a hemostyptic agent since the late sixties. Collagen is the most frequent structural protein in all mammalians. The monomeric protein of approximately 300 kDa (tropocollagen) is covalently crosslinked at specific sites. The mature protein is therefore insoluble and forms characteristic fibrils with high tensile strength. Numerous sub-classes of collagen have been described, the most common of which is collagen type I, the main collagen type in skin, tendons bones and cornea. Collagen is a fibrous protein consisting substantially of a triple helix with a length of approximately 290 nm. Five of these triple helices (tropocollagen molecules) are staggered to form a microfibril with a diameter of approximately 3.6 nm. These microfibrils have polar and non-polar segments that are readily accessible for specific inter- and intrafibrillar interactions. Microfibrils are packed into a tetragonal lattice to form subfibrils with a diameter of about 30 nm. These subfibrils are then assembled into the collagen fibril, the basic unit of connective tissue, which has a diameter of several hundred nm and is therefore visible in a light microscope as a thin line, see reference 1. Collagen gel and collagen sponge, as produced during the manufacturing process, comprises these fibrils as the smallest units, as proved by microscopy.

Collagen may be used as a material for sealing wounds, possibly with a coating comprising a fibrin glue. Fibrin glues i.e. the combination of fibrinogen, thrombin and aprotinin have successfully been used therapeutically for many years for gluing tissues

and nerves and for sealing surfaces when there is minor bleeding. On draw back of the fibrin glues has been that in cas of major bleeding the glue is usually washed away before sufficient polym risation of fibrin has occurred. To ov rcome this problem surgeons have manually applied liquid fibrin glues to absorbable carriers such as collagen fleece.

Despite the impressive success of these combined applications this method has not been applied on a broad scale, due to some disadvantages. The preparation is relatively cumbersome, the method requires experience and skilled personnel, and the preparation is not readily available in cases of emergency, the time for preparation being in the range of 10 to 15 min. These factors stimulated the development of an improved product resulting in the development of a fixed combination of a collagen carrier covered with a coating of solid fibrinogen, solid thrombin and solid aprotinin as disclosed in EP 0 059 265. The product disclosed in EP 0 059 265 which has been marketed under the trademark TachoComb® can be applied directly to the wound. When the coating comes into contact with aqueous fluids like blood, other body fluids or saline, the components dissolve and fibrin is formed. The product is applied to the wound with a slight pressure and collagen is tightly bound (glued) to the injured surface. Haemostasis is achieved and the wound is sealed.

Beside some blood coagulation stimulating activity, the function of collagen in TachoComb® is mainly that of a carrier which adsorbs and confers mechanical stability to the coagulation preparation with which it is coated. Other advantages of collagen, in particular in the form of a sponge, are its biodegradability, its relatively high tensile strength, even in the wet state, its high resistance against the penetration of liquids and air, and its high flexibility in the wet state.

The present invention is primarily concerned with the production of a collagen sponge which may be used as a carrier for fibrinogen, thrombin and/or aprotinin, e.g., as in TachoComb®. The collagen sponge may also be used directly, i.e. without a coating, as a bandage on topical injuries, for support of haemostasis, such as for prevention of rebleeding, for weak, diffuse bleeding from parenchymatic organs, for application on burns, skin grafts, Dekubitus or skin defects, or as a bandage on topical injuries.

In the prior art, a number of methods for preparing a collagen carrier have been suggested. WO 86/05811 discloses a weighted microsponge for immobilizing bioactive

materials in motive bioreactor systems, the microsponge comprising a highly cross-linked collagen matrix. The highly cross-linked collag n matrix is prepared by milling a source of Type I, II or III collagen to yi ld fibers having a diameter on the order of 1 to 50 μm and a length no greater than 200 μm. The milled collagen is formed into a soluble collagen dissolved in a solvent, or an insoluble collagen dispersed in a solvent by admixture with a solvent, such as acetic acid, lactic acid, proprionic acid or butyric acid. In the case of a collagen dispersion, the mixing is accomplished with a high level of agitation using a blender, so as to produce microfibers of the collagen. Next, a weighting additive is blended with the collagen-liquid mixture and the composite mixture is formed into small droplets and solidified by freezing. A number of techniques for producing small particles are disclosed. The frozen composite is vacuum freeze-dried, the combination of freezing and drying being referred to as lyophilization. The freeze-dried collagen matrix composite is treated so as to cross-link the collagen. The collagen can be cross-linked using either chemical cross-linking agents, by severe dehydration at an elevated temperature or by a combination. The collagen matrix aimed at being resistant to collagenase and other enzymatic degradation thereby making these materials particularly suitable for culturing organisms. After washing the cross-linked collagen matrix, the microsponges may be sterilized and aseptically packaged. In the weighted microsponge, the collagen matrix has an open to the surface pore structure with an average pore size in the range of from about 1 to about 150 μm, the pores of the matrix occupying from about 70 to about 98% by volume of the microsponge. The microsponge further has an average particle size of from about 100 to about 1000 μm and a specific gravity of above about 1.05. The weighting material may be metal or alloys from metal, metal oxides and ceramics.

US 5,660,857 discloses a process for preparing a composite comprising an insoluble protein matrix and an oleaginous material, which is useful as a material for surgical dressings and biomedical implants, and as a cosmetic material for application to the skin. The process of US 5,660,857 comprises the steps of mixing a protein, the oleaginous material and water to form an emulsion of the oleaginous material in an aqueous dispersion of the protein, and subsequently drying or freeze-drying the emulsion to form a film or a sponge. The insoluble fibrous protein is predominantly comprised of insoluble collagen, which may suitably be obtained from bovine skin. In one embodiment, the collagen may be swollen in lactic acid prior to use.

WO 99/13902 discloses a method for producing a meningeal tissue growth matrix

comprising the step of preparing physiologically compatible collagen which is substantially free of activ virus s and prions. The collagen is form d into a film, a spong , a non-woven collag n or a felt. The collagen is obtained by a process comprising cleaning skin, tendons, ligaments or bone of fat. The material is then subjected to an enzyme treatment, whereby the collagen material is swelled. The collagen material is then further swollen with an acid solution. The collagen mixture is then homogenised. The product obtained may be a matrix provided in the form of a collagen sponge, a non-woven matrix, felt or film, or a composite of two or more of he foregoing forms. A collagen sponge can be provided by adaptation of the methods for forming collagen sponges disclosed in US 5,019,087. The sponge can be prepared by lyophilization of a collagen dispersion prepared according to WO 99/13902. The sponge density achieved is said to be about 0.1 mg/cm^3 to about 120 mg/cm^3. According to the disclosure of WO 99/13902, the pore size ranges from about 10 µm to about 500 µm. Laminate type of collagen sponge and collagen film are mentioned.

US 5,618,551 relates to a non-crosslinked an potentially crosslinkable pepsintreated collagen or gelatin powder modified by oxidative cleavage in an aqueous solution, which is soluble at an acid pH and stable on storage at a temperature of below 0°C for at least one month. The patent further relates to a process of preparing the powder, comprising preparing an acidic solution of pepsin-treated collagen, subjecting the acidic aqueous solution at room temperature to controlled oxidation, precipitating the oxidized and noncrosslinked pepsintreated collagen at an acid pH, and isolating, concentrating and dehydrating the noncrosslinked pepsintreated collaged so as to obtain it in the form of a reactive acidic powder, and freezing and storing the obtained reactive acidic powder at a temperature of below 0°C.

DESCRIPTION OF THE INVENTION

It has been found that the successful coating of a collagen sponge with a fibrin glue preparation depends on the texture of the collagen sponge. It is thus an object of the present invention to provide a method of producing a collagen sponge with a certain texture, in particular with the aim of making the collagen sponge suitable for coating with a fibrin glue preparation, so as to obtain a material for healing and sealing wounds. It is a further object of the invention to provide a method of producing a collagen sponge having improved physical characteristics in relation to prior art sponges, in the sense of improved

humidity, lasticity, density and elasticity module. It is a further object of the invention to provide a method for preparing a collagen sponge which is air and liquid tight in the sense that, once the collagen sponge is applied to a wound, it will not allow air or liquid to soak through the collagen sponge. It is a still further object of the invention to provide a wound closing material which can be used in gastrointestinal funnels or trachea.

Thus, in a first aspect the invention provides a method of preparing a collagen sponge, comprising the steps of:

- preparing a collagen gel,
- mixing air into the collagen gel, so as to obtain a collagen foam,
- drying the collagen foam, so as to obtain a dry block of collagen sponge having chambers therein,
- isolating, from the block of collagen sponge, parts of sponge with a chamber diameter of more than 0.75 mm and less than 4 mm, or having a chamber diameter average of at most 3 mm.

In the present context, the term "chamber diameter" should be understood as the largest straight-line wall-to-wall distance in a chamber, i.e. as the largest diagonal straight-line distance of a chamber. The chambers may be of a polygonal shape, such as of an octagonal shape.

It has been found that a chamber diameter of more than 0,75 mm and less than 4 mm, or a chamber diameter average of at most 3 mm, renders the collagen sponge particularly useful for being coated with a fibrin glue preparation. Preferably, the collagen gel has a dry mass in the range of 2-20 mg dry mass per 1 g gel, such as 4-18 mg, such as 5-13 mg, such as 6-11 mg per 1 g gel. The dynamic viscosity of the collagen gel is preferably 2-20 Ncm, such as 4-10 Ncm, such as 6-8 Ncm. The collagen sponge preferably has a water content of not more than 20%, such as 10-15%, such as about 18%. The elasticity module of the collagen sponge is preferably in the range of 5-100 N/cm, such as 10-50 N/cm, and the density of the sponge is preferably 1-10 mg/cm^3, such as 2-7 mg/cm^3.

It has been found that a collagen sponge prepared by the method according to the invention is air and liquid tight in the sense that, once the collagen sponge is applied to a wound, it will not allow air or liquid to soak through the collagen sponge. This effect is primarily achieved due to the fact that the step of mixing air into the collagen gel provides

a collagen sponge which has a three-dimensional structure with stacked chambers separated and substantially totally enclosed by walls of collagen material, in contradiction to those known collagen sponges which have fibre structure.

The collagen gel preferably comprises collagen type I material from mammalian, transgenic or recombinant sources. The collagen may comprise material from tendons selected from the group consisting of equine tendons, human tendons, and bovine tendons. The collagen gel may additionally or alternatively comprise recombinant collagen material.

The step of preparing the collagen gel preferably comprises the steps of:

- storing the tendons at a temperature between -10°C and -30°C, and peeling the tendons,
- removing of foreign protein from the tendons,
- reducing of germ content in the tendons,
- swelling of the tendons,
- homogenising of the swelled tendons.

The steps of storing, peeling, removing protein, reducing of germ content, and swelling aim at purificing the raw material, whereas the step of homogenising aims at obtaining the collagen in the form of a gel.

The step of reducing of germ content preferably comprises adding an acid, such as an organic acid, such as lactic acid to the tendons. Further, an organic solvent, such as an alcohol, such as ethanol is preferably added to the tendons. Further, the step of swelling of the tendons preferably comprises adding lactic acid to the tendons. The lactic acid used may be a 0.40 - 0.50% lactic acid, such as a 0.45% lactic acid.

The step of swelling of the tendons may comprise storing the tendons at a temperature of 4°C to 25°C, such as a temperature of 10°C to 20°C, for a period of 48 to 200 hours, such as a period of 100 to 200 hours.

The step of homogenising the swelled tendons is preferably carried out so as to obtain a particle size of collagen gel fragments, i.e. fibre balls, with a diameter of 0.8 - 1.2 cm, such approximately 1 cm. Further, the physical characteristics of the collagen gel are preferably

as stated abov . Th appropriate characteristics may for example be achieved by performing the step of homogenising the swelled tendons by means of a toothed disk mill or adequate homogenisation equipment.

The step of mixing air into the collagen gel preferably comprises the steps of:
- mixing ambient air into the gel by means of a mixer so as to generate a collagen foam,
- feeding the mixed gel foam into a fractionising channel,
- separating collagen gel and collagen foam contained in the fractionising channel.

At least some of the collagen gel separated from the collagen foam in the fractionising channel may be led back to the mixer. In that case, the ratio between the amount of collagen gel which is led back to the mixer from the fractionising channel and the amount of fresh collagen gel led to the mixer is preferably between 0.1 and 0.5. The step of separating collagen gel and collagen foam preferably comprises the steps of:
- separating a selected part of the collagen foam contained in the fractionising channel,
- leading the selected part of the collagen foam out of the fractionising channel for drying thereof.

In a preferred embodiment of the method, a temperature of 15°C to 40°C, such as 20°C to 25°C is maintained in the fractionising channel.

Subsequent to mixing air into the collagen gel, the collagen foam may be homogenised for a period of 2 to 4 minutes.

Prior to the step of drying the collagen foam and subsequent to the step of mixing air into the collagen gel, a neutraliser may be added to the collagen foam, and the collagen foam is preferably neutralised in order to arrive from a pH-value of, usually, between 2.5 and 3.5 to a pH-value in the collagen foam between 6.5 and 8.5. A neutraliser comprising an ammonia solution may be used, and the collagen foam is preferably neutralised for a period of 5-30 hours, such as 10-20 hours, such as approximately 24 hours.

Prior to the step of drying the collagen foam, the collagen foam is preferably filled into a drying container in such a way that substantially no air is drawn into the foam while filling.

The step of drying preferably comprises drying at a temperature between 15°C and 60°C, such as betw en 20° and 40°C, for a period of 50-200 hours, such as 100-150 hours, so as to obtain a dry collagen sponge. The drying may be performed at a pressure slightly under atmospheric pressure, such as at a pressure of between 700 and 900 mbar, such as approximately 800 mbar.

The collagen sponge produced by the method according to the invention preferably fulfils at least one of the following criteria:

- pH-value between 5.0 and 6.0,
- lactic acid content at the most 5%,
- ammonium content at the most 0.5%,
- soluble protein content, calculated as albumin content, at the most 0.5%,
- sulphate ashes content at the most 1.0%,
- heavy metal content at the most 20 ppm,
- microbiological purity, at the most 10^3 CFU/g,
- collagen content of 75% to 100%,
- density of 1-10 mg/cm^3, such as 2-7 mg/cm^3,
- elasticity module of 5-100 N/cm, such as 10-50 N/cm.

The step of isolating parts of collagen sponge may comprise dividing the collagen sponge into a plurality of parts by cutting. The parts obtained may be shaped in any desirable form, such as conical, cylindrical, including cylindrical with an annular cross-section, rectangular, polygonal, cubic, or they may be transformed into a granulate by an appropriate granulating method etc.

In a second aspect, the present invention relates to a method of preparing a collagen sponge, comprising the steps of:

- preparing a collagen gel,
- mixing air into the collagen gel, so as to obtain a collagen foam,
- drying the collagen foam, so as to obtain a dry block of collagen sponge having chambers therein,
- isolating, from the block of collagen sponge, parts of sponge having the following properties:
  - elasticity module in the range of 5 to 100 N/cm,
  - density in the range of 1 to 10 mg/cm^3,

- chamber diameter of more than 0.75 mm and less than 4 mm, or a chamber diameter average of at most 3 mm.

It should be understood that any and all steps of the method according to the first aspect of the invention may also be performed in the method according to the second aspect of the invention. Further, any and all characteristics and features of the collagen sponge produced by the method according to the first aspect of the invention may also be achieved by the method according to the second aspect of the invention.

In a third aspect, the present invention provides a device for extracting a part of a collagen foam and for degenerating another part of the collagen foam to a collagen gel, comprising:

- a fractionising channel comprising an inlet for receiving a flow of collagen foam, an outlet for a part of the flow of collagen foam, and a bottom portion which is inclined downwards in the direction of the flow of collagen foam,
- at least one outlet for collagen gel at the bottom portion of the fractionising channel,

wherein the position of the outlet is movable in a vertical direction at an end of the fractionising channel.

In a fourth aspect, the present invention provides an elongated collagen sponge having a through-going hole or bore and a flexible wall. In a preferred embodiment, such a collagen sponge may be used closing wounds or re-establishing gastrointestinal funnel and trachea walls in mammalians. Thus, the collagen sponge may have circular or elliptical cross-section. The collagen sponge may be applied both as an filling, or as in a gastrointestinal funnel, or as an outer sleeve applied to an outer surface of a gastrointestinal funnel.

The inner diameter of the through-going hole or bore may, for application in various human gastrointestinal funnels and trachea, for example be as follows:

Bowels:	0,5 - 6 cm
Rectum:	1 - 4 cm
Large intestine:	2 - 6 cm
Small intestine:	0.5 - 3 cm
Oesophagus:	0.5 - 2 cm
Trachea:	1 - 4 cm

The collag n spong may, e.g., be used for closing wounds after surgical removal of outpouchings on gastrointestinal funn l walls, such as after rectal surgery, such as after surgical removal of hemorrhoids. Examples of indications made possibl by the collagen sponge according to the invention are:

- wound dressing,
- support of haemostasis, such as
  - weak, diffuse bleeding from parenchymatic organs,
  - surgical procedures on surgery locations where ectrosurgery or ligation has been performed prior to application of the collagen sponge,
  - prevention of rebleeding (securing of sutures),
  - application on burns,
  - bandage on topical injuries,
- drug delivery, such as delivery of antibiotics.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1 and 2 contain a flow chart illustrating the steps involved in a preferred embodiment of the method according to the invention,

Fig. 3 is a photography of the surface of a collagen sponge produced by a method according to the invention (courtesy Prof. Dr. Roman Carbon, Chirurgische Univ. Klinik Erlangen, Germany).

DESCRIPTION OF THE DRAWINGS

In a preferred embodiment, the invention comprises the following steps as illustrated in Figs. 1 and 2:

Step 1 Delivery of deep-frozen horse tendons

The horse tendons are delivered and stored at -18 °C to -25 °C.

Step 2 Peeling of horse tendons

In a half-frozen state, the thin skin of the tendons is manually removed with a knife. Th

tendons are then again deep-frozen at -18 °C to -25 °C.

Step 3 Mechanical slicing of peeled hors tendons

Optionally, peeled frozen tendons are disinfected for 30 min in 70 % ethanol and passed into production rooms under ethanol. The tendons are then washed, and after washing the tendons are compacted to blocks and deep frozen at -18 °C to -25 °C. The frozen tendon blocks are then sliced with a cutting machine with a rotating knife into slices having a thickness of approximately 1 mm.

Step 4 Washing and disinfection of the tendon slices

In order to remove soluble proteins, the tendon slices are first soaked in water for injection for 3 - 6 hours, then washed with water for injection or demineralized water until the supernatant is free of hemoglobin. The tendon slices are then disinfected in 70 % ethanol for 15 min and washed twice in 0.45 % lactic acid in drinking water (sterile filtered and depyrogenised) to remove the ethanol.

Step 5 Production of collagen gel

The washed tendon slices are soaked in 0.45 % lactic acid for 2-5 days, preferably 4 days, and then homogenised to a collagen gel. Exposure to 0.45 % lactic acid is considered to be the main virus inactivation step.

Step 6 Foaming

With dissolver stirrers sterile filtered air is whipped into the collagen gel. The arising foam is fractioned, and the fraction with a bubble size of 1 - 3 mm is collected. The foam is poured from the steel container into a barrel which is slowly rotated for approximately 3 minutes to obtain a homogeneous foam. This foam is filled into drying containers. The base of the container consists of a textile tissue which is permeable to fluids, so as to allow draining of the foam. After 5 - 24 hours, preferably 18-24 hours, the drained foam is exposed to ammonia gas generated from a 26 % ammonia solution of DAB quality. During this process, the surplus of ammonia shifts the pH of the foam to the alkaline region. Ammonia is removed during the subsequent drying process resulting in a neutral product.

Step 7 Drying the foam

The foam is dried in warm air in a high grade steel drying chamber for 48 - 150 hours, preferably 120 - 150 hours. The result is collagen sponge shaped in blocks.

Step 8 Cutting the collagen blocks

The cutting is performed with a vertical cutting machine. First, the sides of the block are cut off to yield a block with vertical sides with a side length of 50 cm. This block is then cut vertically into 4 bars with a width of 11 cm. The bars are again trimmed at their upper and their lower side and then sliced into strips with dimensions of 50 x 11 x 0.4 - 0.7 cm. The weight of the collagen sponge strips preferably takes into account any specification of collagen in the final product to be achieved, such as TachoComb® H, TachoComb® and Tachotop®.

Step 9 Sorting the collagen sponge strips

The collagen sponge strips are then subjected to a visual control. Strips with one or more of the following defects are discarded:

- strips with an average chamber diameter smaller than 1 mm or larger than 3 mm
- strips with inhomogeneous chamber structure
- strips with holes (single chambers with a depth larger than the thickness of the sponge)

The sorted strips are stored for maximally 1 year in airtight, disinfected light metal containers at a temperature of 15 - 25 °C.

Fig. 3 is a photography of the surface of a collagen sponge produced by a method according to the invention, the photography being taken at a magnification factor of approximately 20,000 (courtesy Prof. Dr. Roman Carbon, Chirurgische Univ. Klinik Erlangen, Germany). The surface shown in the photography of Fig. 3 is a surface of a cross-sectional cut in a collagen sponge prepared by a method according to the present invention. The dark areas in the photography represent chambers, while the light areas in the photography represent collagen material, including walls of collagen material separating the chambers.

REFERENCES

1. Baer, E. Gathercole, L.J. and Keller, A., *Structure hierarchies in tendon collagen: an interim summary,* Proc. Colston Conf., 1974, 189; Hiltner, A. Cassidy, J.J. and Baer, E., *Mechanical properties of biological polymers,* Ann. Rev. Mater. Sci., 15, 455, 1985)

CLAIMS

1. A method of preparing a collagen sponge, comprising the steps of:
- preparing a collagen gel,
- mixing air into the collagen gel, so as to obtain a collagen foam,
- drying the collagen foam, so as to obtain a dry block of collagen sponge having chambers therein,
- isolating, from the block of collagen sponge, parts of sponge with a chamber diameter of more than 0.75 mm and less than 4 mm, or with a chamber with an average diagonal dimension of 3 mm.

2. A method according to claim 1, wherein the collagen gel comprises collagen type I material from mammalian, transgenic or recombinant sources.

3. A method according to claim 2, wherein the collagen comprises material from tendons selected from the group consisting of equine tendons, bovine tendons and human tendons.

4. A method according to claim 2 or 3, wherein the step of preparing the collagen gel comprises the steps of:
- storing the tendons at a temperature between -10°C and -30°C, and peeling the tendons,
- removing of foreign protein from the tendons,
- reducing of germ content in the tendons,
- swelling of the tendons,
- homogenising of the swelled tendons.

5. A method according to claim 4, wherein the step of reducing of germ content comprises adding an acid and an organic solvent to the tendons.

6. A method according to claim 5, wherein acid is an organic acid, such as a lactic acid.

7. A method according to claim 5 or 6, wherein the organic solvent is an alcohol, such as ethanol.

8. A method according to any of claims 4-7, wherein the step of swelling of the tendons comprises adding of lactic acid to the tendons.

9. A method according to any of claims 4-8, wherein the acid has a pH value in the range of 1 to 4, such as 1.5 to 3.5, such as 2.5 to 3.0.

10. A method according to any of claims 4-9, wherein the lactic acid is a 0.45% lactic acid.

11. A method according to any of claims 4-10, wherein the step of swelling of the tendons comprises storing of the tendons at a temperature of 4°C to 25°C for a period of 48 to 200 hours.

12. A method according to claim 11, wherein the tendons are stored for a period of 100 to 120 hours.

13. A method according to any of claims 4-12, wherein the step of homogenising the swelled tendons comprises obtaining a substance comprising particles of tendons, the particles having a length or diameter of 0.8 to 1.2 cm.

14. A method according to any of claims 4-13, wherein the step of homogenising the swelled tendons comprises obtaining a substance having a viscosity of 2 to 20 Ncm.

15. A method according to any of claims 4-14, wherein the step of homogenising the swelled tendons is carried out by means of a toothed disk mill.

16. A method according to any of the preceding claims, wherein the collagen gel has a dynamic viscosity of 2-20 Ncm.

17. A method according to any of the preceding claims, wherein the step of mixing air into the collagen gel comprises the steps of:

- mixing ambient air into the gel by means of a mixer so as to generate a collagen foam,
- feeding the mixed gel foam into a fractionising channel,
- separating collagen gel and collagen foam contained in the fractionising channel.

18. A method according to claim 17, wherein at least some of th collagen g l separated from the collagen foam in the fractionising channel is led back to the mixer.

19. A method according to claim 18, wherein the ratio between the amount of collagen gel which is led back to the mixer from the fractionising channel and the amount of fresh collagen gel led to the mixer is between 0.1 and 0.5.

20. A method according to any of claims 17-19, wherein the step of separating collagen gel and collagen foam comprises the steps of:

- separating a selected part of the collagen foam contained in the fractionising channel,
- leading the selected part of the collagen foam out of the fractionising channel for drying thereof.

21. A method according to any of claims 17-20, further comprising maintaining a temperature between 15°C and 40°C in the fractionising channel.

22. A method according to any of the preceding claims, further comprising, subsequent to mixing air into the collagen gel, homogenising the collagen foam for a period of 2 to 4 minutes.

23. A method according to any of the preceding claims, further comprising, prior to the step of drying the collagen foam and subsequent to the step of mixing air into the collagen gel, adding a neutraliser to the collagen foam and neutralising the collagen foam in order to achieve a pH-value in the collagen foam between 6.5 and 8.5.

24. A method according to claim 23, wherein the neutraliser comprises an ammonia solution.

25. A method according to claim 23 or 24, wherein the collagen foam is neutralised for a period of 5-30 hours.

26. A method according to claim 25, wherein the collagen foam is neutralised for a period of 20-30 hours.

27. A method according to any of the preceding claims, wherein th step of drying comprises drying at a temp rature between 15°C and 60°C for a period of 48-200 hours, so as to obtain a dry collagen sponge.

28. A method according to claim 27, wherein the step of drying is carried out at a pressure of 700 to 900 mbar.

29. A method according to any of the preceding claims, wherein the step of drying comprises drying at a temperature between 15°C and 40°C for a period of 100-200 hours.

30. A method according to any of the preceding claims, wherein the collagen sponge fulfils at least one of the following criteria:

- pH-value between 5.0 and 6.0,
- lactic acid content at the most 5%,
- ammonium content at the most 0.5%,
- soluble protein content, calculated as albumin content, at the most 0.5%,
- sulphate ashes content at the most 1.0%,
- heavy metal content at the most 20 ppm,
- microbiological purity, at the most 10^3 CFU/g,
- collagen content of 75 to 100%,
- density of 1 to 10 mg/cm^3,
- elasticity module in the range of 5-100 N/cm.

31. A method according to any of the preceding claims, wherein the collagen sponge has a water content of not more than 20%.

32. A method according to any of the preceding claims, wherein the step of isolating parts of collagen sponge comprises dividing the collagen sponge into a plurality of parts by cutting.

33. A method of preparing a collagen sponge, comprising the steps of:

- preparing a collagen gel,
- mixing air into the collagen gel, so as to obtain a collagen foam,
- drying the collagen foam, so as to obtain a dry block of collagen sponge having chambers therein,

- isolating, from the block of collagen sponge, parts of sponge having the following properties:
  - elasticity module in the range of 5 to 100 N/cm,
  - density in the range of 1 to 10 mg/cm^3,
  - chamber diameter of more than 0.75 mm and less than 4 mm, or a chamber diameter average of at most 3 mm.

34. A method according to claim 33, comprising the steps of any of claims 1-32.

35. A device for extracting a part of a collagen foam and for degenerating another part of the collagen foam to a collagen gel, comprising:
- a fractionising channel comprising an inlet for receiving a flow of collagen foam, an outlet for a part of the flow of collagen foam, and a bottom portion which is inclined downwards in the direction of the flow of collagen foam,
- at least one outlet for collagen gel at the bottom portion of the fractionising channel, wherein the position of the outlet is movable in a vertical direction at an end of the fractionising channel.

36. An elongated collagen sponge having a through-going hole or bore and a flexible wall.

37. An elongated collagen sponge according to claim 36 and having a circular or elliptical cross-section.

38. An elongated collagen sponge according to claim 36 or 37, and having outer dimensions allowing the sponge to used for closing wounds or re-establishing walls in a mammalian gastrointestinal funnel or trachea system.

39. An elongated collagen sponge according to any of claims 36-38, wherein the bore or hole has diagonal dimensions corresponding to the inner or outer cross-sectional dimensions of mammalian gastrointestinal funnels or tracheas.

40. An elongated collagen sponge according to claim 38 or 39 having outer dimensions corresponding to the inner dimension of the human rectum, so as to make the sponge suitable for closing wounds in the rectum wall or re-establishing the rectum wall.

Process	Added material
Step 1 **Delivery of** **deep-frozen horse tendons** Storage of tendons at -18 °C to -25 °C Controls: appearance, ash, degradability by collagenase	
↓	
Step 2 **Peeling of horse tendons** Storage of peeled tendons at -18 °C to -25 °C	
↓	
Step 3 **Slicing of peeled horse tendons** Disinfection of tendons with 70 % ethanol Washing of tendons with water Deep-freezing Slicing	70 % ethanol ← water for injection ←
↓	
Step 4 **Washing and disinfection of tendon slices** Washing with water Disinfection with 70 % ethanol Washing with 0.45 % lactic acid	water for injection ← 70 % ethanol ← 0.45 % lactic acid ←
↓	

Fig. 1

Process (continued) | **Added material**

Step 5

Production of collagen gel ← 0.45 % lactic acid

Soaking of tendon slices ← 0.45 % lactic acid

Homogenisation of tendon slices

↓

Step 6

Foaming ← sterile air

Whipping of air into the collagen gel

Fractionation of the foam

Homogenisation of the foam

↓

Step 7

Drying of collagen foam

Draining of the foam ← NH_3

Neutralisation of the foam with NH_3

Drying of the foam

IPC: weight of dried collagen sponge blocks

↓

Step 8

Cutting of collagen sponge blocks to strips

IPC: weight of collagen sponge strips

↓

Step 9

Sorting the collagen sponge strips according to structural properties

Fig. 2

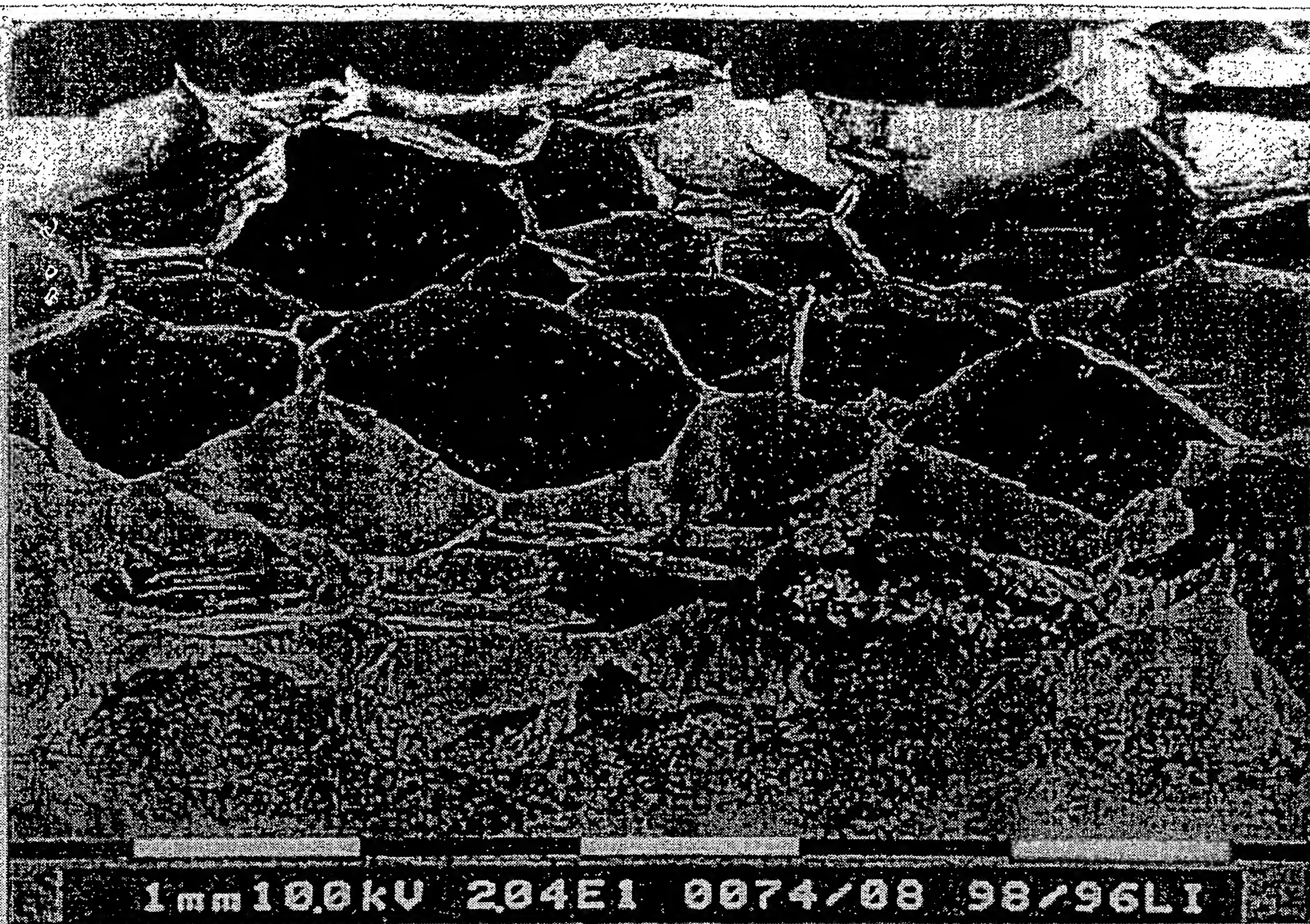

Fig. 3